

1995 WILLIAM ALLAN AWARD ADDRESS

Human Genetics: A Discipline at Risk for Fragmentation

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This is my 40th anniversary as a member of the American Society of Human Genetics. I attended my first meeting as a Fellow in 1956. At the time, I was working with several large families to study the mode of inheritance of familial hypercholesterolemia and other hyperlipidemias. That meeting was held at the University of Connecticut in Storrs. As had been the custom in those early days, we met in conjunction with the American Institute of Biological Sciences and had the opportunity to interact with a number of other groups of geneticists dealing with organisms as diverse as tomatoes, corn, drosophila, and mice. Although this was the ninth annual meeting of the American Society of Human Genetics, we still considered ourselves very much a part of the greater genetics community. The officers and the great majority of the few members that we had were Ph.D.s—many from the field of population genetics and others from various aspects of basic genetics, such as Curt Stern, then the President-Elect. The President of the Society was Sheldon Reed, who was principally responsible for making us aware of the relatively new concept of genetic counseling. The meeting consisted of all the 15 submitted papers and a symposium on presenile dementia. The first paper, given by Elaine Amiden, was entitled, “Attitudes and Information about Human Heredity Among Social Workers.” I believe that this was the initial attempt at introducing patient-oriented health professionals with master’s degrees to our field. The expansion of this important group, which I will return to later, is obvious from the large number of genetic counselors who are now members of the Society. Among the other papers, the majority were examples of what I consider the fundamental basis of our discipline of human genetics. If we define genetics as the study of heritable variation, human genetics is the study of such variation in our own species. I will return later to the importance of this concept and its central position in our discipline.

Some of the papers in that 1956 meeting related to topics such as variation in amino acid metabolism, fatty acid metabolism, and blood groups. Two of the papers of prophetic importance were one by Buckwalter on “a genetic reference for human disease” and one by Newton Morton on “a critical review of autosomal and partial sex linkage in man.” McKusick’s catalog and the current major activities in linkage mapping are some of the present activities following these earlier papers. The symposium considered physical, biochemical, and biological variables in Alzheimer disease, which is still confounding us by its variability.

The next meeting I would like to recall for you is that of 1963, when I was Chairman of the Program Committee, which had as its other members O. J. Miller and Paul Marks. The three of us met in our living room for one afternoon to construct the program—a bit different from the current large committee with its meetings, conference calls, faxes, and large FedEx packages. We had received 70 abstracts but found that we only had room for the presentation of 51 papers. Until 1962, every paper submitted was presented from the platform. It was felt that, if you thought you had something to say, you should be given the opportunity either to impress the membership or to be shot down.

Our small committee spent most of its time arguing whether we should for the first time plan concurrent sessions or be hardnosed and designate 19 abstracts to be read by title only. Rightly or wrongly, we chose the latter option. How unimportant this debate seems now in light of the submission to the 1995 meeting of 2,021 abstracts, the existence of 304 slide presentations, divided into 28 concurrent sessions, 1,438 posters, symposia, workshops, and 279 papers read by title only. These numbers are but one indication of the phenomenal success story of this Society. Annual dues in 1963 were \$10.00, and registration was \$3.00. Considering that dues increased by 50% to \$15.00 by 1969, it can be calculated that a projection of dues to 1995 would lead to \$88.60, while the same projection would predict a registration fee for 1995 of \$26.10. In fact, our dues this year are \$105.00, close to the projection, which reflects both the fiscal responsibility of our treasurers and the successful income of the *Journal*. On the other hand, registration is \$160.00, about six times the pro-

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jected amount. I am sure that many factors are responsible for this discrepancy, and it may be worthwhile for our Board to consider this problem as it relates to the difficulty of our many young members and nonmembers in these stressful fiscal times.

The 1963 meeting under the Presidency of Jim Crow still had a majority of Ph.D.'s on the Board of Directors. Many of the papers continued to discuss human genetic variation, now using more sophisticated biochemical and immunological techniques; included were a number of papers in cytogenetics, mostly stressing chromosome variation and new technology for the accurate study of chromosomes; early studies in pharmacogenetics as a first approach to environmental factors in the manifestation of genetic variation; and a few early attempts at gene mapping. Because we met back-to-back with the International Conference on Birth Defects, we were able to present a symposium on recent developments of human genetics in Europe, which allowed our members to be educated by some of the leaders in human genetics around the world.

By the time of the 1963 meeting, my own activities included clinical cytogenetics, in which we were fortunate to be able to describe some new abnormalities. We also were involved in basic studies concerning stimulation of lymphocytes, the cells used for cytogenetic studies, including the first evidence that these cells had memory and the discovery of the mixed lymphocyte reaction.

My next memorable meeting was in 1969 when I was honored by the Society electing me as its President for that year. We had received 134 abstracts, of which 71 were presented. Since posters had not yet been invented, we scheduled three simultaneous sessions for one afternoon, had 63 papers read by title only, and had two plenary sessions and a symposium consisting of five totally unrelated papers—one of which was on thalassemia, one on linkage, one on secondary sex ratios, one on an enzyme deficiency, and one of the first papers on prenatal diagnosis, specifically for Tay Sachs disease. The three simultaneous sessions were on, respectively, biochemical genetics, population genetics, and clinical genetics. The two plenary sessions were on the same general categories and included the relatively new field of somatic cell genetics. It was at this meeting that I persuaded the Board of Directors to establish a Social Issues Committee, which has become an important activity for the Society.

I have two particularly vivid recollections of that meeting in San Francisco. The first was Jérôme Lejeune's William Allan Award address, entitled "The National Institute of Death," in which he accused us of encouraging abortion by our studies of prenatal diagnosis. This debate continues to plague us; most recently in the continuing ban on federally funded fetal research, which is of great importance in our growing understanding of

developmental genetics. My second memory is the Board of Directors meeting held on a high floor of the Sheraton Hotel—the only tall building that remained standing after the 1906 earthquake. When I stepped from the elevator, people were running around the halls in great excitement and informed me that there had been a strong earthquake, which I had not felt in the elevator. We held the meeting anyway, but after about an hour or more, the room began moving violently with an aftershock. The members of the Board ran out of the room, leaving only Jim Neel and me to wonder where they were going. The meeting ended at that point, with Jim turning to me and saying, "Kurt, God is trying to tell us something about the length of this meeting," a duration that seems quite reasonable by today's criteria of multiple multi-hour Board meetings.

By the time of this meeting, our laboratory had become involved in the study of early chromosomal changes induced by SV40, recently confirmed by Jim Neel for other polyoma viruses. We also found unusual *in vitro* lymphocyte responses in such diseases as rheumatic fever, a disease involving gene-environment interactions. In cytogenetics, we were one of two groups showing chromosome instability in Fanconi anemia. We showed the power of long-term lymphoid cell cultures for genetic studies and, in biochemical genetics, began a long and fruitful collaboration with Rochelle Hirschhorn on the examination of acid alpha-glucosidase in Pompe disease.

Both the Board and the membership in 1969 were fairly evenly divided between M.D.'s and Ph.D.'s, and the field of medical genetics had begun to flourish. Nevertheless, it remained clear to the entire membership that we were engaged in a common goal of studying the genetic aspects of human variation. Regardless of the type of doctoral degree, we remained a friendly, interactive group who attended, with great interest, each other's papers. During the 60s and early 70s, our medical colleagues became the majority of the membership, to be joined in the next decade by a large influx of genetic counselors into the Society. Beginning in the middle 80s, we began to see and hear from the new specialty of molecular genetics and were able to avoid a serious threat of fragmentation by convincing our new colleagues to join the Society rather than forming their own. Two smaller groups have appeared at the meetings more recently—those concerned with gene therapy and representatives from industry. The latter influence initially led to loud debates at our business meetings and was perceived as a potential threat to the survival of university-based laboratories. While this concern is still an issue, many have recognized the inevitability of commercial activities in the field, particularly with the rapidly growing opportunities for screening and therapy. Some of these early perceptions of competition within

the Society became accentuated with the formation of several new organizations. Even before these new entities were formed, some of us had become concerned with the risk of fragmentation, which we felt, and I still feel, were due to losing our concentration on our common goal of maintaining the discipline of human genetics regardless of which new tools became available and became more and more powerful.

In 1980, I was privileged to be a Founding Member of the American Board of Medical Genetics. While we recognized the necessity of certifying people in the various clinical and laboratory subtopics of human genetics, we fully agreed on the necessity of an examination in general human genetics in order to be sure that all who became certified remained well versed in our central discipline. The Board has held fast to this concept, despite the growth of the subspecialties and the addition of a new one. I believe that this action was instrumental in slowing down the trend toward fragmentation.

In 1992, I became a Founding Member of the American College of Medical Genetics. While the purpose of the College is to allow medical genetics to join the mainstream of clinical practice in this country, if for no other reason than appropriate recognition and reimbursement by all payers, many of us remain concerned about this split between the discipline of human genetics and its clinical application. Even within the College, there is a division between clinical and laboratory activities, although the leadership has expended a great deal of effort in maintaining a common ground. At about this time, with the acceptance of the American Board of Medical Genetics as a primary board by the American Board of Medical Specialties, we were unfortunately forced to separate the growing group of master's degree genetic counselors, who, in turn, formed their own Board. I believe that this split is a most unfortunate omen of further fragmentation.

Parenthetically, I would like to give a few words of unsolicited advice to our younger members who are M.D.'s or M.D./Ph.D.'s, especially fellows in training. Don't be misled by those who are so enchanted by the new tools, especially molecular biology, that they tell you that you cannot succeed unless you spend 100% of your time working in the laboratory. As clinician/scientists, it is your obligation to spend some significant time, say 20%–25%, in direct patient contact. Without this clinical activity, you will lose the critical opportunity to bring new questions from the patients and their families to the laboratory and to return with answers to benefit your study subjects. You owe yourselves the exciting but humbling experience of helping patients and can only benefit our discipline by personal observation and clarification of human variation. For example, current theoretical, laboratory, and animal model work on strategies for gene therapy will only become meaningful

for the physicians among you if you can apply these in a thoughtful, humane manner by direct contact with the subjects exposed to these hopeful, but still highly experimental, techniques. Those of you who choose to do primarily clinical genetics should not be put off by the current difficulties in obtaining funding for clinical research. There will continue to be sources of money for well-designed clinical investigation, especially in collaboration with the appropriate basic scientists or epidemiologists.

The increasing development of separate identities for the subfields of human genetics seriously needs to be controlled by our common theme. To me, the clear responsibility of the Society is not to lose sight of and to sustain this unifying force in order to avoid the gradual balkanization of human genetics. This is becoming even more urgent with the recent growth in the number of training programs, some concentrating on the science and others on the clinic. The latter has become even more obvious with the recent establishment of residencies in clinical genetics. In training our young successors, we must continue to differentiate tools such as molecular biology, computer science, cytology, medical practice, and genetic counseling from the formal discipline of human genetics and its various connected branches. If we keep in mind the definition of human genetics as the study of human variation, we will both retain and teach our successors and colleagues the power and beauty of genetic thinking. By this I mean the application of genetic principles to new discoveries ranging from the activities of the Genome Program to the discovery of new types of mutation responsible for disease or disease susceptibility.

Let me illustrate such thinking with a few examples. Early in my career, while using peripheral blood cells for cytogenetic studies, I showed that the dividing cells were peripheral blood lymphocytes. I noticed that, before dividing, these cells resembled those described as responsible for graft versus host disease. By a series of planned and serendipitous experiments, my colleagues and I brought these observations back to genetics by describing the mixed lymphocyte response as a marker of genetic variation between and within families. Another example derives from the genetic application of the study of the mechanism of idiosyncratic responses to medications, which has led to the field of pharmacogenetics. This field is of basic and clinical importance to the vast and often dangerous differences between individuals based on their genetic makeup as it interacts with important environmental agents. As a basic principle, pharmacogenetics is no different from recent findings of the genetic basis for individual variation in response to infectious agents. For example, susceptibility or lack thereof to *Helicobacter* is determined by the ABO/secretor system; that to parvovirus B19 by the P blood

group system; and one form of malaria by the presence or absence of the Duffy blood group antigen.

The study of susceptibility to disease lends itself particularly well to genetic thinking. In the field of atherosclerosis, the old finding of increased susceptibility related to elevated cholesterol levels initially brought about broad recommendations for severe fat restriction in the diet and more recently for the screening of children. Many of us have long tried to stress that use of a severely altered diet should take into consideration individual genetic susceptibility as determined by the several genes responsible for altered lipid metabolism. We have also recommended the restriction of childhood screening to those children with a family history of early heart attacks or hypercholesterolemia. Similar consideration exists in the new field of cancer-susceptibility genes. We are certain to see increasing emphasis on population screening, which as everyone here knows has raised a number of controversies on both ethical and pragmatic grounds. Logical screening programs again should be designed with careful consideration of genetic principles.

Many years ago, Mueller and others voiced great concern about the effects of the treatment of individuals with genetic disease. They feared that treatment would lead to reproduction, which in turn would increase the pool of deleterious genes in the human species. This in turn would have a negative impact on the health and survival of the species. Similar arguments have been made that prenatal diagnosis and selected termination of homozygotes for recessive lethals will increase the frequency of the genes for these conditions, since two thirds of the surviving pregnancies will be heterozygotes for the gene in question, and have a similar detrimental impact as treatment. I remember, many years ago during such a debate, the remarks of Tatum, who used genetic thinking in pointing out the following scenario:

There exists a genetic disease called diabetes, which does not allow normal procreation. Someone discovers insulin and now allows diabetics to live normal lives and to produce normal numbers of offspring. If one such individual is treated, there will come a time when he may have 100 descendants with diabetes. At this point a disaster strikes, and we forget how to make insulin. The hundred diabetics may now die without reproducing. While it is tragic that these 100 people would die young with disease, what is the genetic impact of treating that first diabetic? He will not only have produced over several generations the 100 diabetics but would also have passed on his own normal genes to many hundreds of individuals who will have been selected for survival and have a positive impact on the health of the species.

It is, therefore, not only correct from the point of view of medical ethics to treat as best you can, but in the long run this can only benefit the human race from a genetic point of view. We also are quite ignorant about

potential advantages in our exponentially changing environment of carrying single copies of genes responsible for recessive diseases so that the argument relating to prenatal diagnosis is also somewhat specious. In fact, many of those that decried the possible negative alteration of the human gene pool were also strong believers in positive eugenics, a concept that has not completely dissipated. As I once pointed out a number of years ago in a paper entitled "On Redoing Man," methods of positive eugenics, including planned breeding, artificial insemination of sperm from so-called superior individuals, and, as was predicted then, the possibility of cloning, will lead to increased homozygosity that, in the long run, will be detrimental to the species rather than improving it.

These then are just a few examples of the importance of applying genetic thinking to medical and even societal problems. It is, I believe, this form of thinking, as well as a consistent practice of applying all available and appropriate methods and tools to the study of human variation, that is essential for maintaining the unity of the field of human genetics.

Let me illustrate this principle by continuing a brief review of the work from my laboratory since 1969. In cytogenetics, my colleagues and I continued to describe new abnormalities such as trisomy 22, the first proven pericentric inversion in man and its genetic effect, phenotype/genotype correlation of X chromosomal abnormalities, various aspects of mosaicism, including its familial occurrence, the impact of parental abnormalities on fetal loss, and chromosome abnormalities in neoplasms. We also, by doing a population study, showed that the apparent increase in criminal behavior of XYY individuals could be totally explained by their mental retardation and poor judgment—no different from XY individuals with the same degree of retardation. In biochemical genetics, we worked on normal variations of placental alkaline phosphatase and a variety of inborn errors including, among others, homocystinuria, lysosomal disorders, and Menkes disease. We described a number of new aspects of clinical conditions due to mutant genes and were also involved in some of the early attempts at mapping genes. More recently, we have done work in molecular genetics and the application of *in situ* hybridization to cytogenetics. To me, the importance of this list is the demonstration that one can use such disparate tools as cytology, enzymology, protein chemistry, molecular biology, immunology, cell biology, tissue culture, and epidemiology and yet apply all of these to the study of causes and effects of human variation, the fundamental subject at the basis of our discipline. It also demonstrates that human genetics is an opportunistic science that begins with careful observation of both normal and abnormal human beings with any method available. It is, therefore, my urgent plea that all of us in the

Society continue to exert a serious effort to work with each other and to respect all activities leading to a better understanding of human genetics. Such an effort will, it is hoped, prevent the fragmentation of our discipline.

Finally, I would like to publicly recognize several groups of people who have meant so much to me in my professional life. First, I would acknowledge with gratitude four early mentors (see appendix A). Charles Wilkinson, my first boss, introduced me to family studies in hyperlipidemias, arranged for me to study for a master's degree in genetics with Morris Harnley at NYU, and made it possible for me to do a fellowship in human genetics at the University of Uppsala in Sweden from 1957 to 1958. There I was privileged to work with and learn from Marco Fraccaro, who taught me tissue culture and cytogenetics and who convinced me to enter an academic career in human genetics. Beginning with sabbaticals in his laboratory in 1961 and 1971, and continuing until his recent untimely death, Harry Harris became and remained my constant source of how to think genetically, while being a close and true friend to Rochelle and me. The last of my mentors was the late Horace Hodes, whose Department of Pediatrics I joined in 1966. He taught me respect for patients and families and the clinical and administrative skills that I have tried to apply during my 19 years as his successor.

I have been undeservedly fortunate in having a great support staff (see appendix B), particularly my secretary, lifesaver, and friend of many years, Delores Gray, and

my two successive laboratory assistants, Susan Verbo in the early years and Sophie Paciuc since 1971.

My life in human genetics and in our Society has been a great joy, primarily because of the many wonderful friends, colleagues, and collaborators with whom I have interacted over the years. Although there are many others, these ten have been constant and personally very close (see appendix C). First and foremost of these is Rochelle Hirschhorn, my wife, friend, and supporter, who tries her best to keep me on a straight path. Bob Desnick, with whom I have had a wonderful, interactive relationship at Mount Sinai for the past 18 years, has given me the opportunity, beginning this year, once again to devote myself fully to human genetics. The others on the list know what we mean to each other.

Finally, and most important to me, is the group of 60 trainees who have spent significant time working with me (see appendix D). Among them are department chairmen, division chiefs, professors, basic scientists, clinical investigators, lawyers, and clinicians practicing medical genetics. If any others feel that they should be on this list, please forgive my mental lapse. I consider these wonderful people my greatest contribution and know that they will sustain the tradition of carrying on their work with human genetics as their guiding principle.

I will end by expressing my deep gratitude to the Awards Committee and to the American Society of Human Genetics for the greatest honor I will ever receive, recognition from my peers in the form of the Allan Award.

Appendix A

Mentors

Charles Wilkinson
Marco Fraccaro
Harry Harris
Horace Hodes

Appendix B

Supporters

Delores Gray
Susan Verbo
Sophie Paciuc

Appendix C

Long-Term Collaborators/Colleagues

Rochelle Hirschhorn
Robert Desnick
Maimon Cohen
Henry Nadler
Michael Kaback
Lillian Hsu
Lynn Godmilow
David Rimoin
Emmanuel Shapira
Primarosa Chieri

Appendix D

Trainees

Fritz Bach
Marilyn Bailin
Marcello Barcinski
Nicholas Beratis
Navah Bloch-Shtacher
Gunther Brittinger
Susan Broder
Patrice Chernay
Lawrence Chessin
Elaine Conod
James Conover
Herbert Cooper
Andrea Cramer
Cesare Danesino
Karen David

Steven Douglas
Lester Firschein
Jeffrey Flier
Lynn Fleisher
Debra Freedenberg
Melvin Gertner
Philip Glade
Jessica Grant
Dora Grossman
Harold Grotsky
Nemat Hashem
Peter Hathaway
Jean Hentel
Clement Hsu
Sara Kaffe

Nataline Kardon
Josephine Kerr
Hyon Kim
Boris Kousseff
Gundula LaBadie
Ernest Lieber
Mark Ludman
Lloyd Mayer
Carmen Merryman
Kyoshi Oikawa
Peter Papenhausen
Rena Petrella
Seth Pincus
Peter Price
David Rassin

Orlando Rendon
Carolyn Ripps
Rochelle Seide
Donna Shanies
Lawrence Shapiro
Susan Sklower
Moyra Smith
Eva Sujansky
Michael Swift
Brian Turner
Gary Vorsanger
William Waithe
Judith Willner
Lawrence Wisniewski
Joseph Zelson